Progress report

Antibiotics in the treatment of biliary infection

Bile is difficult to obtain for culture in man. Because of this, antibiotic treatment of biliary infection is often directed towards biliary organisms which are suspected, rather than proven. To complicate effective treatment further, infection may be asymptomatic, presenting with septic complications following a surgical or radiological procedure.

Despite knowledge of the pattern of infection in biliary disease, the microorganisms involved, and the spectrum and pharmacokinetics of potentially effective antibiotics, bacteria are often difficult to eradicate from the bile and biliary surgery has a high incidence of septic complications. There have been few reviews of this subject, particularly incorporating recent data, and a reassessment is necessary. This paper describes the clinical and bacteriological aspects of biliary infection, and the excretion and efficacy of specific antibiotics in bile. Based on the information available a therapeutic strategy is proposed.

Biliary infection

DEFINITION

Ideally biliary tract infection should be defined by the organism count in bile. Keighley *et al*[1] reported finding at least 10^5 organisms per ml in over 90% of positive peroperative bile cultures, and this count could be taken as diagnostic. Such a definition is, however, impracticable because bile is difficult to collect. Although biliary sepsis is diagnosed clinically when there are systemic signs of infection combined with features of biliary tract disease, organisms may be cultured from bile in the absence of symptoms. Thus the ideal definition of biliary infection should be based on the number of organisms isolated from bile, but in practice this is rarely possible.

CLINICAL ASPECTS

Organisms may be cultured from gall bladder and common bile duct bile, or from liver biopsy tissue in normal patients.[2] Although these organisms may represent the normal hepatobiliary flora, some may be caused by contamination of the specimen during collection.[3] Gall bladder bile from patients with acute and chronic cholecystitis yields organisms in 30–50% of patients.[4] Positive culture is more frequent in acute rather than chronic disease and in those with an obstructed as opposed to patent cystic duct.[5] The incidence of positive culture from bile duct bile is greatest (75–100%) when obstruction is caused by a calculus or stenosis of a surgical anastomosis.[6][7] In patients with bile duct obstruction owing to carcinoma of the pancreas or bile duct, without previous surgery, the incidence of positive culture is lower, in most reports below 10%.[4]

ORGANISMS

These are predominantly the aerobic enteric organisms *E coli, Klebsiella spp,* and *Streptococcus faecalis. Pseudomonas aeruginosa* is rarely present except after invasive non-surgical biliary procedures.[8] Anaerobes, particularly *Bacteroides spp* and *Clostridia spp*, may be isolated from approximately 40% of infected bile samples[9] and are cultured more frequently from patients who have had multiple biliary operations or bile duct/bowel anastomoses.[10] They are more difficult to isolate than aerobes and adequate transport and culture techniques are necessary. Pure anaerobic infection is unusual, mixed infection with aerobes being the rule.

SOURCE OF INFECTION

This is not known. Under experimental conditions bacteria carried to the liver in portal venous blood may be cultured from the bile.[11] Whether this route is important in the pathogenesis of biliary infection is uncertain, as portal venous blood from patients without intestinal disease is usually sterile.[12] Also if such a mechanism were responsible, the incidence of biliary infection should be similar in malignant and calculous bile duct obstruction.

Ascending infection from the duodenum may be responsible. The higher incidence of infection in patients with calculous obstruction, has been attributed to incomplete bile duct obstruction, and used to support this hypothesis.[6] Although high counts of colonic bacteria are present in the duodenum in patients with liver disease,[13] however, the normal adult duodenum contains only a small number of organisms, which are not common biliary pathogens.

COMPLICATIONS OF INFECTION

Gram negative septicaemia may complicate biliary infection at any time, but occurs particularly after surgery or non-surgical invasive procedures such as cholangiography.[4] Surgical risks such as endotoxic shock, acute renal failure,[14] wound sepsis[15] and subphrenic abscess, are increased in the presence of biliary infection. Longstanding infection of the gall bladder with *Salmonella spp* has been suggested in the pathogenesis of carcinoma of the gall bladder.[16]

Antibiotic secretion into bile

Although the complications of biliary infection may be prevented by therapeutic levels of an appropriate antibiotic in the serum, the eradication of organisms from the bile depends upon effective biliary antibiotic concentrations. Knowledge of the secretion of antibiotics into bile and of their efficacy once there should be helpful in choosing the best therapeutic regime.

GENERAL PRINCIPLES

Factors which influence the extent of biliary secretion of all compounds include molecular weight, polarity and hepatic metabolism. The role of each of these factors, however, is not clear cut and no absolute rules exist. In general, below a certain molecular weight (mw), which in man is 500–600, biliary secretion is poor and urinary excretion predominates.

Thus rifamide (mw 811) and erythromycin (mw 734) are well secreted in bile while cycloserine (mw 102) is not. Although oxidation may increase the polarity of lipid-soluble antibiotics and glucuronide formation increases the molecular weight, hepatic metabolism may reduce the antibacterial activity.[17]

Despite advances in the understanding of transport mechanisms across the hepatocyte, the pathways taken by antibiotics are not clear. Whatever the mechanisms may be, however, only 1% of a 1 gram dose of antibiotic need enter the normal daily output of bile (approximately one litre) to attain a mean concentration of 10 μg/ml. This, for most current antibiotics would be inhibitory for the majority of susceptible bacteria. As a general rule the biliary concentrations of all antibiotics are reduced in the presence of abnormal liver function tests, and no antibiotic is known to enter the bile when there is complete bile duct obstruction.

METHODS OF STUDY

Although there are many reports of biliary antibiotic excretion in man, differences in dose, route of administration and timing of samples, together with lack of clinical details of the patients studied make comparisons of the data difficult. Measurement of biliary antibiotic concentrations on spot samples, for example from the gall bladder at surgery, are of limited value. A complete profile of biliary and serum concentrations can only be made in patients with biliary drainage by T-tube, percutaneous transhepatic catheter or transpapillary nasobiliary tube. Aspiration of duodenal juice may be used, but the bile is unavoidably contaminated.

SECRETION OF SPECIFIC ANTIBIOTICS (TABLE 1)

Rifamycins

Although these compounds are excreted extremely well in bile,[18] rifamide, the most thoroughly studied, is no longer available for clinical use. Rifampicin has not been evaluated in the treatment of biliary infection.

Erythromycin

While erythromycin is well excreted in bile, minimum inhibitory concentrations (MICs) for aerobic gram negative organisms are only exceeded

Table 1   *Biliary excretion of antibiotics into common bile duct bile in man, in the absence of biliary obstruction or abnormal liver function tests*

Poor (bile/serum ratio <1)	Moderate (bile/serum ratio 1–4)	Good (bile/serum ratio>4)
Ticarcillin	Ampicillin	Mecillinam
	Carbenicillin	Mezlocillin
Cephazolin		Piperacillin
Cefotaxime		
Ceftazidime		Cefamandole
Cefuroxime		Cefoperazone
Sulphamethoxazole	Trimethoprim	
		Rifampicin
Amikacin	Metronidazole	Erythromycin
Gentamicin	Clindamycin	Tetracyclines

after high doses.[19] Moreover, erythromycin appears to be less active in bile compared with other test media.[20]

Tetracyclines

Biliary concentrations may be up to 30 times those in serum.[21] Tetracycline, however, has up to 1000 times less antimicrobial activity in human bile than in broth,[22] and recent data suggest that doxycycline is less effective in clearing sensitive bacteria from bile than mezlocillin or cefotaxime.[23] The increasing incidence of resistant strains, particularly of enteric organisms, makes the blind treatment of biliary infection with tetracycline unreliable.

Penicillins

Ampicillin concentrations in bile are greater than those in serum in patients with normal liver function, and exceed the MICs for most biliary pathogens for several hours after the administration of normal doses.[24] Biliary levels are greater after oral rather than parenteral drug. Esters of ampicillin (pivampicillin, talampicillin) and amoxycillin are better absorbed from the gastrointestinal tract than ampicillin, and produce higher biliary concentrations.[25]

Mecillinam, an amidino-penicillin, has greater activity against gram negative bacilli than gram positive cocci but is inactive against all anaerobes. Biliary concentrations are sufficient to kill most isolates of *E coli, Klebsiella spp* and *Proteus spp*, but not of *Strep faecalis*.[26]

Carbenicillin and ticarcillin have activity against *Ps aeruginosa* as well as the other biliary pathogens, but after 1 gram of carbenicillin the MIC for *Ps aeruginosa* is not always exceeded by the concentrations found in bile.[17] Ticarcillin is two to four times more active *in vitro* against *Ps aeruginosa*, but biliary concentrations have not been studied in detail. One report indicates concentrations below those in serum in patients with normal liver function tests.[27]

The ureidopenicillins, mezlocillin, azlocillin and piperacillin, also have a broad spectrum of activity and are effective against *Ps aeruginosa* and some pathogenic anaerobes. Mezlocillin excretion in bile is greater than that of ampicillin, amoxycillin and carbenicillin and may exceed 20% of the total dose given in patients with normal liver function.[28] [29] In jaundiced patients, in whom bile duct obstruction has been relieved, mezlocillin still achieves therapeutic biliary concentrations,[30] and eradicates bacteria.[23] Piperacillin has greater antibacterial activity than mezlocillin and is excreted in bile to the same degree.[31]

Cephalosporins

Despite the continual appearance of new analogues, none yet are active against *Strep faecalis*. Of the parenteral preparations cephazolin,[32] cefuroxime,[33] and cefamandole[34] are active against the other common biliary pathogens. Cefotaxime,[35] cefoperazone,[36] and ceftazidime[37] also have activity against *Ps aeruginosa*. In patients with normal liver function, biliary concentrations of the older preparations are approximately equal to those in serum. The biliary excretion of cefoperazone and cefamandole is much greater. Of the orally active cephalosporins, the biliary recovery of cephalexin is greatest.[29]

Co-trimoxazole

The combination of trimethoprim and sulphamethoxazole has a spectrum covering the common aerobic biliary pathogens. In anicteric patients, trimethoprim concentrations in bile are two to three times those in serum, while the bile to serum ratio for sulphamethoxazole is 0·1–1·0.[38] The biliary concentrations of trimethoprim are well above the MICs for aerobic biliary organisms, but synergy between trimethoprim and sulphamethoxazole would not be expected.

Aminoglycosides

Biliary concentrations of gentamicin and amikacin sulphate are about half those in serum,[39] [40] and are above the MICs of most biliary pathogens, except *Ps aeruginosa*. One report, however, has shown that gentamicin therapy does not reduce bacterial counts in infected bile, [41] despite the apparent therapeutic concentrations present and the higher antimicrobial activity of aminoglycosides in bile compared with broth.[22]

Nitroimidazoles

Metronidazole and traces of its metabolites are found in bile[42] and in a jaundiced patient with external bile drainage, biliary and serum concentrations were above the MIC of anaerobic organisms for 24 hours after an intravenous infusion of 500 mg (personal communication).

Clindamycin and Lincomycin

Although these are active against anaerobes and are well excreted in bile,[44] they are not widely used probably because of their association with pseudomembranous colitis and the availability of other effective anti-anaerobic agents.

Chloramphenicol

Although 2·7% of a 1 gram dose of chloramphenicol appears in human bile, only 5% of this is microbiologically active, and the concentrations are inadequate to inhibit common biliary pathogens.[45]

Fusidic acid

Although well excreted in bile, 95% is inactive metabolite.[46]

ANTIBIOTIC CHOICE

The efficacy of antibiotics in the treatment of biliary infection depends on more than the extent to which they are excreted in bile. Other important factors include the antimicrobial potency of individual compounds, and the effect of bile on antibacterial activity. Table 2 shows that although mezlocillin is well excreted in bile compared with cefotaxime, these antibiotics are similar in the degree to which they exceed the MIC of *E coli*, because of cefotaxime's greater potency. Ideally, the choice of antibiotic for the treatment of biliary infection should depend on a knowledge of the biliary and tissue concentrations achieved compared with the MICs for the organisms isolated or suspected. Such data are difficult to assemble.

Of the oral compounds co-trimoxazole, trimethoprim, amoxycillin and cephalexin should be of therapeutic value in anicteric patients. Their value in jaundiced patients is less certain. None are effective against *Ps*

Table 2 *Relationship between peak concentrations of cefotaxime and mezlocillin in bile, and the mean minimum inhibitory concentrations (MICs) for* E coli

	Peak biliary concentration (μg/ml)	Mean MIC for E coli (μg/ml)	Ratio
Cefotaxime (dose 1 g, im)	14	0·06	233
Mezlocillin (dose 5 g, iv)	640	2	320
(Data from references 28, 47, 48, and 49)			

aeruginosa and cephalexin will not kill *Strep faecalis*. The value of tetracyclines is controversial. The cost of trimethoprim and co-trimoxazole is less than that of amoxycillin or cephalexin at the time of writing in our hospital, but local hospital contract prices may alter this position.

Of the parenteral preparations the ureidopenicillins and new cephalosporins, particularly those with high biliary excretion, are best. Despite the lower cost of cephalosporins compared with ureidopenicillins, the latter may be more appropriate because of their availability and effectiveness against *Strep faecalis*. The aminoglycosides, although less costly than ureidopenicillins, do not penetrate bile well, and should be restricted to those patients with septicaemia, in combination with ureidopenicillins or cephalosporins. Metronidazole remains the current choice to supplement therapy if infection is thought to include anaerobes.

Use of antibiotics in biliary tract disease

PROPHYLAXIS

Antibiotic prophylaxis should be considered before biliary surgery, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and non-surgical bile drainage procedures. The goal is to reduce systemic, intraperitoneal and wound sepsis caused by microorganisms released from the biliary tract.

The presence of bacteria in bile is related to postoperative wound infection,[15] which may be reduced by antibiotics given before or during surgery. Ideally only those patients with infected bile should be given preoperative antibiotics. Clinical data which identify such patients are jaundice, recent rigors, emergency operation or surgery within four weeks of emergency admission, previous biliary surgery, common bile duct obstruction, stones in the common bileduct, and age greater than 70 years.[50 51] A controlled trial of prophylactic antibiotics in these high risk patients reduced postoperative wound infection from 27% to 4%.[52] Examination of bile collected by duodenal aspiration preoperatively[53] or by direct puncture of the biliary system at surgery,[54] has been used to identify patients with biliary infection, but neither method is in regular use. Prophylactic antibiotic could be given to all patients before biliary surgery. This approach using a single dose is unlikely to encourage bacterial resistance, but the benefits must be balanced against the risk of toxic and allergic reactions.

Rifamide,[55] gentamicin,[56] cephaloridine,[52] cephazolin,[57 58] co-trimoxazole,[59] and cefamandole[60] all reduce wound infection after biliary

surgery. A single preoperative dose of antibiotic is effective,[57–59] and in one study the results were no better when antibiotic was continued postoperatively.[57] Metronidazole has no beneficial effect.[61] The most appropriate choices at present seem to be cephazolin, cefamandole or co-trimoxazole.

For high risk patients having ERCP, PTC and interventional radiological procedures, antibiotic prophylaxis is appropriate. The overall incidence of cholangitis after ERCP is 0·8%[62] but is greater in patients with biliary obstruction.[63] Percutaneous transhepatic cholangiography with the Chiba needle is followed by fever and bacteraemia in approximately 2·5% of patients, and cholangitis and sepsis in 1%.[64] The addition of antibiotic to radiocontrast media for ERCP has been advocated[65] but a limited trial has shown no benefit.[66] It is important to realise that premedication with antibiotic will not necessarily prevent septicaemia. Other factors including the avoidance of high biliary pressures during injection of radiocontrast medium for PTC, ERCP and T-tube or operative cholangiography,[67] and the thorough cleaning of endoscope and catheter before ERCP,[68] must be recognised in order to reduce the risk of septic complications. In the absence of data, the choice of antibiotic for these procedures is wide. We use one of the new cephalosporins or an ureidopenicillin.

Whether antibiotics should be continued after surgical or non-surgical intervention depends upon the clinical situation. Despite the results of controlled studies showing the benefit of single dose prophylaxis against wound sepsis, more prolonged administration is warranted after reconstructive biliary surgery when the bile is found to contain micro-organisms. Similarly after PTC or ERCP, if gram stain or culture of bile taken at the time of the procedure is positive and/or bileduct obstruction is present, antibiotics should be continued until sepsis has been treated or obstruction relieved. There are no strict rules governing the duration of therapy under these circumstances. It must be stressed that early biliary decompression must be considered in patients with bile duct obstruction after cholangiography to reduce the risk of cholangitis and septicaemia; antibiotic administration alone is incomplete management.

TREATMENT
When acute cholecystitis is suspected, and blood has been taken for culture, antibiotics are started while the diagnosis is confirmed. The choice of antibiotic ranges from a parenteral cephalosporin or ampicillin, to combined therapy with an ureidopenicillin and aminoglycoside. The regime chosen is governed by the severity of the clinical picture.

Acute suppurative cholangitis with biliary obstruction has a high pre and postoperative mortality[69] and demands comprehensive antibiotic treatment followed by biliary decompression. Initial treatment is usually started without knowledge of the organism responsible, and the antibiotic(s) given must have a broad spectrum to cover all possible pathogenic organisms. A combination of ureidopenicillin – for example, mezlocillin, or cephalosporin – for example, cefotaxime, with an amino-glycoside is used. Metronidazole may be added to cover the possibility of anaerobic infection. The regime is adjusted when the results of blood culture are known. Septicaemia should be treated with antibiotics and intravenous fluids before bile duct drainage. The best method for

decompressing the biliary tract is controversial, and will depend on local expertise. Surgery has now been challenged by percutaneous catheter drainage and endoscopic sphincterotomy. The endoscopic approach should produce fewer blood/bile fistulae than percutaneous transhepatic bile duct catheterisation or surgery.

Recurrent cholangitis in patients with multiple biliary operations is often caused by partial obstruction which cannot be improved by further surgery. The patients are ambulant and hospital admission for each attack is not practical. Oral antibiotics may be prescribed at home. Co-trimoxazole, trimethoprim alone, cephalexin and amoxycillin are the best available oral antibiotics. For the reasons already discussed, the value of tetracycline is debatable. No trial data for these patients exist, and the only report of benefit has been for co-trimoxazole.[70] Avoidance of foods, especially salads, which may harbour pathogenic bacteria, may be valuable.[71]

Conclusion

Bile is difficult to collect for culture in man, and this underlies the problem of treating biliary infection effectively. Much is known of the bacterial flora of the biliary tract and of the excretion and activity of antibiotics in bile. Less is known of the efficacy of different antibiotics for biliary infection, but the new techniques of non-surgical biliary drainage are already providing useful data. When the pathogenic organism is known, the therapeutic choice is relatively straightforward. In the absence of this information, no therapeutic regime is without criticism, but the following suggestions are based on our present knowledge.

Prophylaxis – for surgery (single dose with premedication): cephazolin 1 g im, or co-trimoxazole (160 mg trimethoprim and 800 mg sulphmethoxazole) iv, or cefamandole 1 g iv.

Prophylaxis – for other invasive procedures (single dose 0·5 hours before procedure): mezlocillin 2–5 g iv infusion, or cefotaxime 1 g iv.

Acute cholecystitis – septicaemic patient: mezlocillin 5 g iv 8 hourly, or cefotaxime 1 g iv 6 hourly, plus gentamicin 80 mg im 8 hourly, plus metronidazole 400 mg orally 8 hourly, or 500 mg iv 8 hourly.

Acute cholecystitis – milder illness: cephazolin 1 g im 6–8 hourly, or ampicillin 1 g im 6–8 hourly.

Acute cholangitis: mezlocillin 5 g iv 8 hourly, or cefotaxime 1 g iv 6 hourly, plus gentamicin 80 mg im 8 hourly, and metronidazole 500 mg iv 8 hourly.

Recurrent cholangitis (oral therapy): co-trimoxazole 960 mg bd, or amoxycillin 250 mg tds, or cephalexin 250 mg qds, or trimethoprim 200 mg bd.

Apart for prophylactic use, antibiotic therapy is usually continued for

7–10 days. These suggestions are made to stimulate research towards better treatment for biliary infection. The limits of our knowledge on many aspects of this subject are apparent and further study to correct this defect is required.

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References

1 Keighley MRB, Drysdale RB, Quoraishi AH, Burdon DW, Alexander-Williams J. Antibiotics in biliary disease: the relative importance of antibiotic concentrations in the bile and serum. *Gut* 1976; **17**: 495–500.
2 Edlund YA, Mollstedt BO, Ouchterling O. Bacteriological investigation of the biliary system and liver in biliary tract disease correlated to clinical data and microstructure of the gallbladder and liver. *Acta Chir Scand* 1958; **116**: 461–76.
3 Nielsen ML, Justesen T, Asnaes S. Anaerobic bacteriological study of the human liver – with a critical review of the literature. *Scand J Gastroenterol* 1974; **9**: 671–7.
4 Flemma RJ, Flint LM, Osterhout S, Shingleton WW. Bacteriologic studies of biliary tract infection. *Ann Surg* 1967; **166**: 563–70.
5 Dye M, MacDonald A, Smith G. The bacterial flora of the biliary tract and liver in man. *Br J Surg* 1978; **65**: 285–7.
6 Scott AJ, Khan GA. Origin of bacteria in bileduct bile. *Lancet* 1967; **2**: 790–2.
7 Jackaman FR, Hilson GRF, Lord Smith of Harlow. Bile bacteria in patients with benign bile duct stricture. *Br J Surg* 1980; **67**: 329–32.
8 Stille W. Bacteriological studies on bile. In: Classen M, Geenen J, eds. *Proceedings of International Symposium: non-surgical biliary drainage.* Stockholm: Thieme, 1982. (In press.)
9 England DM, Rosenblatt JE. Anaerobes in human biliary tracts. *J Clin Microbiol* 1977; **6**: 494–8.
10 Bourgault AM, England DM, Rosenblatt JE, Forgacs P, Bieger C. Clinical characteristics of anaerobic bactibilia. *Arch Intern Med* 1979; **139**: 1346–9.
11 Dineen P. The importance of the route of infection in experimental biliary tract obstruction. *Surg Gynecol Obstet* 1964; **119**: 1001–8.
12 Orloff MJ, Peskin GW, Ellis HL. A bacteriologic study of human portal blood: implications regarding hepatic ischaemia in man. *Ann Surg* 1958; **148**: 738–46.
13 Martini GA, Phear EA, Ruebner B, Sherlock S. The bacterial content of the small intestine in normal and cirrhotic subjects: relation to methionine toxicity. *Clin Sci* 1957; **16**: 35–51.
14 Pitt HA, Cameron JL, Postier RG, Gadacz TR. Factors affecting mortality in biliary tract surgery. *Am J Surg* 1981; **141**: 66–72.
15 Keighley MRB, Lister DM, Jacobs SI, Giles GR. Hazards of surgical treatment due to microorganisms in the bile. *Surgery* 1974; **75**: 578–83.
16 Welton JC, Marr JS, Friedman SM. Association between hepatobiliary cancer and typhoid carrier state. *Lancet* 1979; **1**: 791–4.
17 Brogard JM, Haegele P, Dorner M, Lavillaureix J. Biliary levels of carbenicillin; experimental and clinical study. *J Int Med Res* 1974; **2**: 142–8.

18 Acocella G, Mattiussi R, Nicolis FB, Pallanza R, Tenconi LT. Biliary excretion of antibiotics in man. *Gut* 1968; **9:** 536–45.

19 Chelvan P, Hamilton-Miller JMT, Brumfitt W. Biliary excretion of erythromycin after parenteral administration. *Br J Clin Pharmacol* 1979; **8:** 233–5.

20 Twiss JR, Berger WV, Gillette L, Aronson AR, Siegel L. The biliary excretion of erythromycin (Ilotycin). *Surg Gynecol Obstet* 1956; **102:** 355–7.

21 Fabre J, Milek E, Kalfopoulos P, Merier G. La cinétique des tétracyclines chez l'homme. *Schweiz Med Wochenschr* 1971; **101:** 593–8, 625–33.

22 Helm EM, Paulus I, Shah PM, Stille W. Antibakterielle Aktivitat von Antibiotika in menschlicher Galle. *Infection* 1976; **4:** 94–101.

23 Helm EB, Wurbs D, Gundlach H, Shah PM, Stille W. Elimination of bacteria in biliary infections under antibiotic therapy. *Drugs Exp Clin Res* 1981; **7:** 349–61.

24 Brogard JM, Pinget M, Meyer C, Dorner M, Lavillaureix J. Biliary excretion of ampicillin: experimental and clinical study. *Chemotherapy* 1977; **23:** 213–26.

25 Kosmidis J, Williams JD, Andrews J, Goodall JAD, Geddes AM. Amoxycillin – pharmacology, bacteriology and clinical studies. *Br J Clin Pract* 1972; **26:** 341–6.

26 Hares MM, Hegarty A, Tomkyns J, Burdon DW, Keighley MRB. A study of the biliary excretion of mecillinam in patients with biliary disease. *J Antimicrob Chemother* 1982; **9:** 217–22.

27 Aikawa N, Ishibiki H, Takami H, Miura S, Kato S. Basic and clinical evaluation of ticarcillin in surgical field. *Chemotherapy (Tokyo)* 1977; **25:** 2699–713.

28 Gundert-Remy U, Forster D, Schacht P. Biliary excretion of mezlocillin in patients subjected to choledochal drainage. *Proceedings 1st International Congress of Mediterranean Society of Chemotherapy* 1978; 575–8.

29 Brogard JM, Kopferschmitt J, Arnaud JP, Dorner M, Villaureix JL. Biliary elimination of mezlocillin: an experimental and clinical study. *Antimicrob Agents Chemother* 1980; **18:** 69–76.

30 Dooley JS, Gooding A, Hamilton-Miller JMT, Brumfitt W, Sherlock S. The biliary excretion and pharmacokinetics of mezlocillin in jaundiced patients with external bile drainage. *Liver* 1983; **3:** 201–6.

31 Giron JA, Meyers BR, Hirschman SZ. Biliary concentrations of piperacillin in patients undergoing cholecystectomy. *Antimicrob Agents Chemother* 1981; **19:** 309–11.

32 Brogard JM, Dorner M, Pinget M, Adloff M, Lavillaureix J. The biliary excretion of cefazolin. *J Infect Dis* 1975; **131:** 625–33.

33 Severn M, Powis SJA. Biliary excretion and tissue levels of cefuroxime. *J Antimicrob Chemother* 1979; **5:** 183–8.

34 Brogard JM, Pinget M, Arnaud JP, Bakich D, Lavillaureix J. The biliary excretion of cefamandole: experimental study and appraisal in humans. *Infection* 1981; **9:** 34–41.

35 Soussy CJ, Deforges LP, Le Van Thoi J, Feghali W, Duval JR. Cefotaxime concentration in the bile and wall of the gallbladder. *J Antimicrob Chemother* 1980; **6** suppl A: 125–30.

36 Marti MC, Farquet C, Fabre J, Rudhardt M. Pharmacokinetics and biliary excretion of cefoperazone in patients with bile duct drainage. *Infection* 1981; **9** suppl 1: S34–6.

37 Gozzard DI, Geddes AM, Farrell ID *et al.* Ceftazidime – a new extended-spectrum cephalosporin. *Lancet* 1982; **1:** 1152–6.

38 Rieder J. Excretion of sulfamethoxazole and trimethoprim into human bile. *J Infect Dis* 1973; **128** suppl: S574.

39 Pitt HA, Roberts RB, Johnson WD. Gentamicin levels in the human biliary tract. *J Infect Dis* 1973; **127:** 299–302.

40 Bermudez RH, Lugo A, Ramirez-Ronda CH, Amadeo JA, Morales J. Amikacin sulphate levels in human serum and bile. *Antimicrob Agents Chemother* 1981; **19:** 352–4.

41 Wacha H, Helm EB. Efficacy of antibiotics in bactobilia. *J Antimicrob Chemother* 1982; **9** suppl A: 131–7.

42 Pieri F, Andre L-J, Abed L. Etude du metabolisme du metronidazole chez l'homme: demonstration de la presence de cet amoebicide dans la bile. *Med Trop (Mars)* 1969; **29:** 375–6.

43 Reference deleted.

44 Sales JEL, Sutcliffe M, O'Grady F. Excretion of clindamycin in the bile of patients with biliary tract disease. *Chemotherapy* 1973; **19:** 11–5.

45 Kunin CM, Glazko AJ, Finland M. Persistence of antibiotics in blood of patients with acute renal failure. II: chloramphenicol and its metabolic products in the blood of patients with severe renal disease or hepatic cirrhosis. *J Clin Invest* 1959; **38:** 1498–508.

46 Godtfredsen WO, Vangedal S. On the metabolism of fusidic acid in man. *Acta Chem*

Scand (B) 1966; **20:** 1599–607.

47 Kosmidis J, Stathakis C, Mantopoulos K, Pouriezi J, Papathanassiou B, Daikos GK. Clinical pharmacology of cefotaxime including penetration into bile, sputum, bone and cerebrospinal fluid. *J Antimicrob Chemother* 1980; **6** suppl A: 147–51.

48 Schrinner E, Limbert M, Penasse L, Lutz A. Antibacterial activity of cefotaxime and other newer cephalosporins (in vitro and in vivo). *J Antimicrob Chemother* 1980; **6** suppl A: 25–30.

49 Wise R, Andrews JM. Activity of mezlocillin against Gram-negative and Gram-positive organisms: comparison with other penicillins. *J Antimicrob Chemother* 1982; **9** suppl A: 1–9.

50 Chetlin SH, Elliott DW. Biliary bacteraemia. *Arch Surg* 1971; **102:** 303–7.

51 Keighley MRB, Flinn R, Alexander-Williams J. Multivariate analysis of clinical and operative findings associated with biliary sepsis. *Br J Surg* 1976; **63:** 528–31.

52 Chetlin SH, Elliott DW. Preoperative antibiotics in biliary surgery. *Arch Surg* 1973; **107:** 319–23.

53 Engstrom J, Hellstrom R, Hogman L, Lonnqvist B. Microorganisms of the liver, biliary tract and duodenal aspirates in biliary diseases. *Scand J Gastroenterol* 1971; **6:** 177–82.

54 Bishop HM, Keighley MRB, Crapp AR, Burdon DW, Slaney G, Alexander-Williams J. Gram stain on bile aspirated at operation: a rational approach to antibiotic therapy in biliary disease. *Gut* 1975; **16:** 841.

55 Bevan PG, Williams JD. Rifamide in acute cholecystitis and biliary surgery. *Br Med J* 1971; **3:** 284–7.

56 Keighley MRB, Baddeley RM, Burdon DW *et al.* A controlled trial of parenteral prophylactic gentamicin therapy in biliary surgery. *Br J Surg* 1975; **62:** 275–9.

57 Strachan CJL, Black J, Powis SJA *et al.* Prophylactic use of cephazolin against wound sepsis after cholecystectomy. *Br J Med* 1977; **1:** 1254–6.

58 Papachristodoulou AJ, Mackenzie A, Norman J, Karran SJ. Single dose cephazolin prophylaxis in biliary tract surgery. *JR Coll Surg Edinb* 1978; **23:** 178–83.

59 Morran C, McNaught W, McArdle CS. Prophylactic co-trimoxazole in biliary surgery. *Br Med J* 1978; **2:** 462–4.

60 Crenshaw CA, Glanges E, Webber CE, McReynolds DB. A prospective randomised double blind study of preventive cefamandole therapy in patients at high risk for undergoing cholecystectomy. *Surg Gynecol Obstet* 1981; **153:** 546–52.

61 Halsall AK, Welsh CL, Craven JL, Hopton DS, Peel RN. Prophylactic use of metronidazole in preventing wound sepsis after elective cholecystectomy. *Br J Surg* 1980; **67:** 551–2.

62 Bilbao MK, Dotter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography (ERCP). A study of 10 000 cases. *Gastroenterology* 1976; **70:** 314–20.

63 Vennes JA, Jacobson JR, Silvis SE. Endoscopic cholangiography for biliary system diagnosis. *Ann Intern Med* 1974; **80:** 61–4.

64 Ott DJ, Gelfand DW. Complications of gastrointestinal radiological procedures: II. Complications related to biliary tract studies. *Gastrointest Radiol* 1981; **6:** 47–56.

65 Jendrzejewski JW, McAnally T, Jones SR, Katon RM. Antibiotics and ERCP: In vitro activity of aminoglycosides when added to iodinated contrast agents. *Gastroenterology* 1980; **78:** 745–8.

66 Collen MJ, Hanan MR, Maher JA, Stubrin SE. Modification of endoscopic retrograde cholangiopancreatography (ERCP) septic complications by the addition of an antibiotic to the contrast media. *Am J Gastroenterol* 1980; **74:** 493–6.

67 Lygidakis NJ. Potential hazards of intraoperative cholangiography in patients with infected bile. *Gut* 1982; **23:** 1015–8.

68 Low DE, Micflikier AB, Kennedy JK, Stiver HG. Infectious complications of endoscopic retrograde cholangiopancreatography. *Arch Intern Med* 1980; **140:** 1076–7.

69 Welch JP, Donaldson GA. The urgency of diagnosis and surgical treatment of acute suppurative cholangitis. *Am J Surg* 1976; **131:** 527–32.

70 Chaudhary S, Turner RB. Trimethoprim-sulfamethoxazole for cholangitis following hepatic portoenterostomy for biliary atresia. *J Pediatr* 1981; **99:** 656–8.

71 Remington JS, Schimpff SC. Please don't eat the salads. *N Engl J Med* 1981; **304:** 433–5.